ST. FRANCIS HOSPITAL NUMBER

DELAWARE STATE MEDICAL JOURNAL

Official Organ of the Medical Society of Delaware

INCORPORATED 1789

VOLUME 26
NUMBER 11

NOVEMBER, 1954

Per Year, $4.00
Per Copy $ .50

CONTENTS

PUBLIC HEALTH ASPECTS OF TUBERCULOSIS IN DELAWARE, *E. W. Hainlen, M.D.*, Wil., Del. 273

MODERN TRENDS, TREATMENT OF PULMONARY TUBERCULOSIS, *Nathaniel Young, M.D.*, Wil., Del. 275

THE SURGERY OF PULMONARY TUBERCULOSIS, *F. T. O'Brien, M.D.*, Wil., Del. 279

DIABETES MELLITUS IN JUVENILE IDENTICAL TWINS, *Edw. M. Bohan, M.D.*, Wil., Del. 285

COLLAGEN DISEASES, *Allen C. Wooden, M.D.*, Wil., Del. 292

CLINICAL EVALUATION OF APPETITE DEPRESSANTS, *C. A. Brusch, M.D., C. W. McClure, M.D., F. A. Straccia, M.D., B. S. Henken, M.S., C. A. Wood, Ph.D., and L. A. Grasse, M.D.*, of Cambridge, Mass. 295

EDITORIALS 297

OBITUARY 298

Entered as second-class matter June 28, 1929, at the Post Office at Wilmington, Delaware, under the Act of March 3, 1879. Editorial Office, 822 North American Building, Wilmington 7, Delaware. Business Office, Farnhurst, Delaware. Issued monthly.


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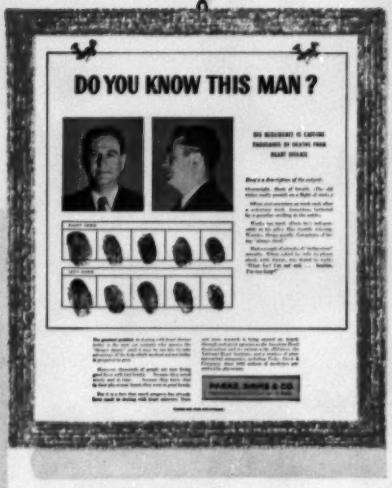
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7. Okey, R.: Cholesterol Content of Foods, J. Am. Dietet. A. *21*:341 (June) 1945.

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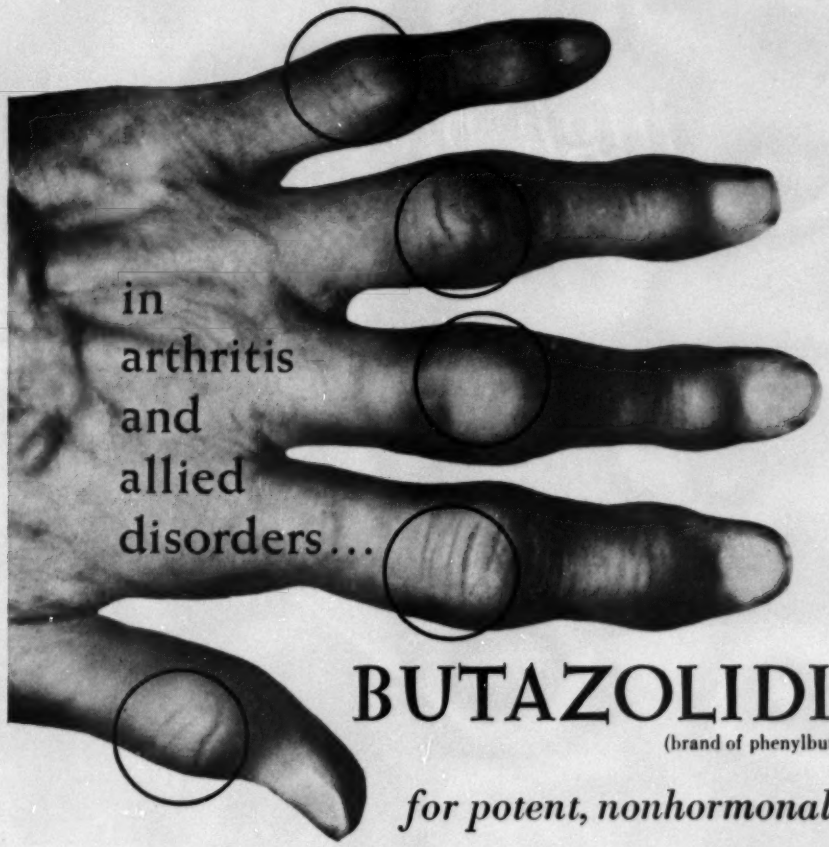

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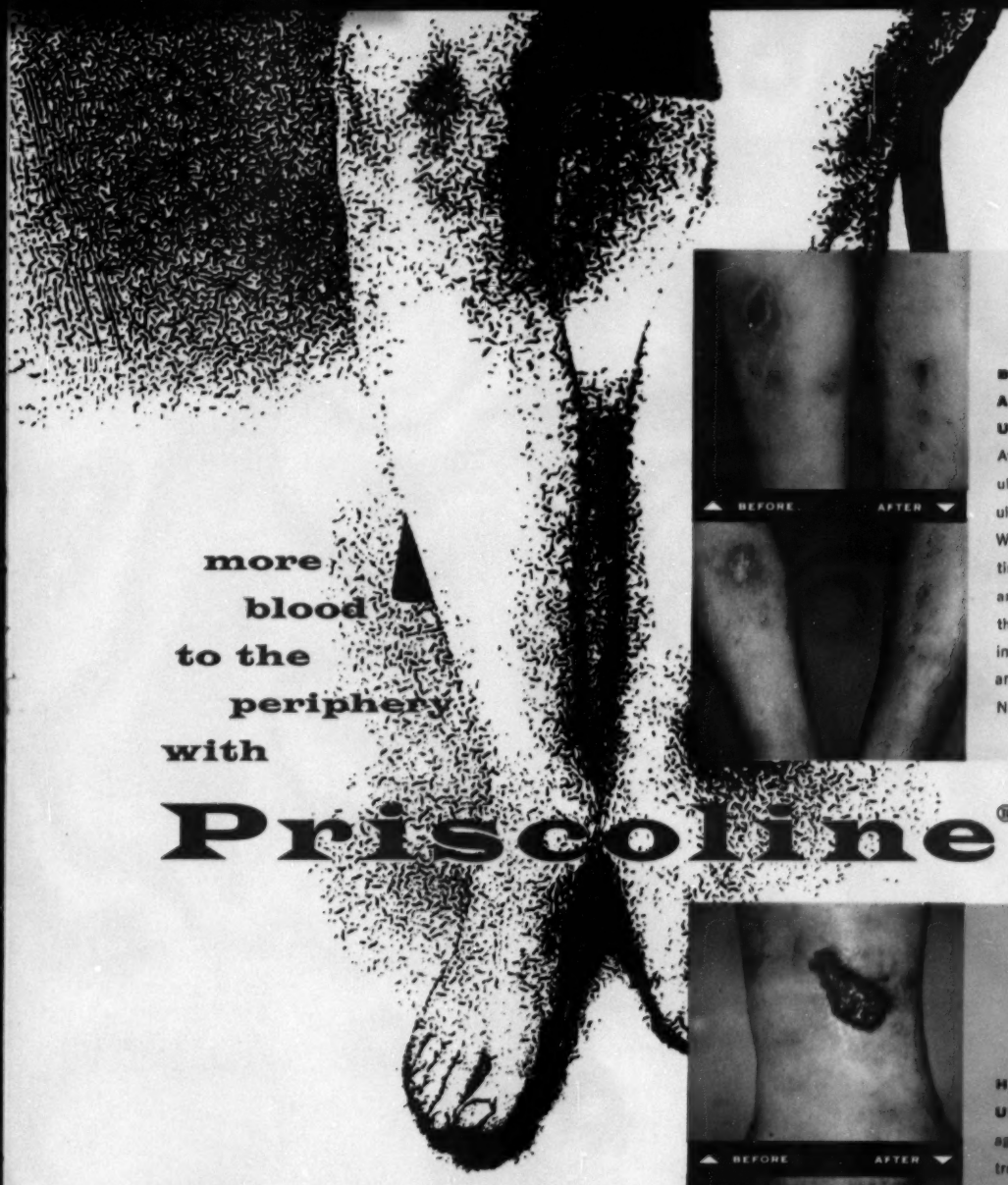

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DELAWARE STATE MEDICAL JOURNAL

Issued Monthly Under the Supervision of the Publication Committee
Owned and Published by the Medical Society of Delaware

VOLUME 26
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NOVEMBER, 1954

Per Year, $4.00
Per Copy 50c

PUBLIC HEALTH ASPECTS OF TUBERCULOSIS IN DELAWARE

E. WILLIS HAINLEN, M.D.*
Wilmington 8, Del.

We, the physicians of Delaware, find ourselves at this juncture in a somewhat advantageous position to make a definite contribution to the study of tuberculosis control. So, too, are the doctors of every other state, but we are a small and compact group that can get results if we will.

Briefly, the position is this. We have recently completed from September, 1953 to January, 1954 the first Statewide Chest X-ray Survey in the country. We started and finished this survey at a time when we had insufficient sanatorium beds to take care of any sudden influx of active cases. In fact we had a small waiting list of patients, predominantly colored, at the time we embarked on the project. We also started at a time when a program of intensive triple antibiotic therapy plus an accelerated surgical attack on a large backlog of cases had been in progress for one year at the sanatorium.

Consequently, we, the medical practitioners of the state, had on our hands within a short space of time, a fairly large and unstudied group of active and potentially active cases of pulmonary tuberculosis, and what is of the broadest significance, the opportunity and the material to observe for some time to come, the effects of domiciliary care and treatment as contrasted with a sanatorium regime. The case load was roughly divided into three groups: those hospitalized as beds became available; those who were attended and supervised by the family physician at home in conjunction with the public health unit nurses; and those who were strictly and solely attended by the private practitioner, or were remotely controlled in the general hospital chest clinics. It is to the physicians in the last two groups that we, as public health administrators, make a special appeal that they contribute to the ultimate sum of our knowledge by recording, or helping to record, (1) the therapeutic regimens used, (2) the degree of patient cooperation, (3) the speed of response to therapy, (4) the duration of the effect, clinically, roentgenologically and bacteriologically, (5) the progress under ambulatory, or combinations of rest and work programs, and (6) the effect on contacts, both intimate and casual. In five years we may have some new ideas, not only about the treatment but also the prevention of tuberculosis. At the date of this paper, only 45 cases from the Survey had been admitted to the sanatorium, so that the remainder constitute a fairly satisfactory control group on the domiciliary side.

One year from the end of the Survey, about January, 1955, we shall increase our sanatorium capacity from 166 to 240 beds, dispense with large open wards, and be able to offer privacy, recreational facilities, rehabilitation and social services, and some other amenities which will make a sanatorium residence and schooling less repugnant and more acceptable to a broader spectrum of patients.

So much for the treatment — but what about the prevention angle? We know, statistically, that the death rate is declining much more rapidly than the case rate, especially since 1947 and the use of streptomycin. Morbidity decrease has always lagged behind mortality decrease, and seven years of antimicrobials seem to have made the ratio even wider, presumably because we have been able to prolong the lives of the "old chronics" and the advanced cases a few years longer, and possibly because in the earlier days of chemotherapy we were prone to use the drugs

* Medical Director, Emily P. Bissell Sanatorium.
Presented at the combined meeting of Wilmington hospitals, St. Francis Hospital, May 25, 1954.

sparingly on minimal cases. Another factor may be the decrease in cases found in the younger age group. In Delaware, for instance, the average age on admission to sanatorium during the past year has been just over 45. Did our younger people forming the bulk of the wage-earning bracket die faster because they postponed sanatorium care for economic reasons?

The apparent lag in the morbidity fall was of considerable concern to a large national group of State Control Officers and Sanatorium Directors who met at Atlantic City in May, 1954. Facts and opinions expressed by each in turn showed an unusual parallelism in view of the differing systems of control used in the various states. Alcoholics, skid-row habituees, and public charges in tuberculosis hospitals show a marked increase, especially in the urban areas. A major change was the advancing age of the tuberculous population. There was a remarkable constancy in the small numbers of minimal cases actually admitted to hospitals. However, the topic of greatest discussion was the impact of drug treatment giving rise to new and different control problems. Home treatment programs that appear to compromise the cardinal principle of isolation cannot gain the acceptance of public health workers. Most of the Control Officers present favored admitting a newly diagnosed patient to a sanatorium initially for complete workup and confirmation of diagnosis, proper orientation of the patient as to the nature of his illness, and initiation of antimicrobial therapy.

When progress was satisfactory and gastric analysis negative, early discharge with rest and drugs at home could be undertaken. Chicago's criteria for discharge specified 50% x-ray clearing, cavity closure by planography, and 24 hour sputum concentrate negative for 10 months, following which there would be clinic maintenance of drug therapy. The large group which satisfied these conditions had a 1% relapse rate, and 2% had an occasional positive concentrate after one year of drug. The maximum hospital benefit group, i.e. the chronics hospitalized 4 to 5 years and still culturally positive, were continued on chemotherapy indefinitely. They had a relapse rate of 11%. In a control group of 500 cases under domiciliary care for 6 months, cooperation was found to be very poor. Many stopped the drug when feeling better and many refused surgical intervention at the optimum time. In general, they refused to submit regular sputum, refused gastrics, and skipped x-rays. There was much apprehension as to whether we were going to be left with a lot of "half-well" patients. The fear of contacts in the home and elsewhere being infected with an antibiotic-resistant organism still exists, since a few cases of such primary infection have already been found.

In the "recalcitrant" group, Connecticut found that 60% were over age 40, and 75% of these were alcoholic. Our situation in Delaware seems to be approximately the same. The question of "locked wards" is ever before us. Many of our neighbor states have legislation covering this problem but it is not too successful. In Delaware we have nothing stronger than home quarantine for our known open recalcitrant cases, a method almost impossible to enforce and, in addition, failing to protect the family.

To quote Dr. Esmond Long as late as May, 1954: "Prevention is based on interruption of contact and stopping dissemination at the source through early detection *and isolation* of cases, fortified on occasion by enhancement of individual resistance through artificial measures, of which BCG vaccination is the best known example." This question of vaccination has been brought up sporadically in Delaware in the past two years. Total population vaccination has only been tried in Scandinavia and with reported success. On this hemisphere only selected groups such as certain American Indian tribes, student nurses and medical students, tuberculosis workers and family groups showing a high predilection have been done. In this state, the policy is still one of watchful waiting with possible use, as Dr. Long puts it, "on occasion". Certainly the benefits of vaccination in the long run are still a matter of controversy among those who are in high-

est authority in the country, particularly those who fear the handicap in case finding by use of the tuberculin test.

A one-year follow-up of the Statewide Survey will soon be available. Following that, and annually for the next 4 years it would be of value if the general practitioners, the Delaware Anti-tuberculosis Society, and the State Department of Health would combine in a thorough study of our results. At the present time the public health nurses are carrying the brunt of post-sanatorium supervision and care, and in the case of the medically indigent, the Delaware Anti-Tuberculosis Society supplies antibiotics to these nurses for use in approved indigent cases. The V.N.A. also cooperates with the private practitioner in dispensing from the same source of supply, to post-sanatorial cases for long term therapy. The only condition imposed is that the patient shall stay in the sanatorium until he has an approved discharge. So far, the results in the way of a decreasing number of relapses seem encouraging.

MODERN TRENDS IN THE TREATMENT OF PULMONARY TUBERCULOSIS

NATHANIEL YOUNG, M.D.,*
Wilmington 8, Del.

The modern trend in the treatment of pulmonary tuberculosis is toward the almost exclusive use of anti-microbial drugs, aided where necessary by surgery.

Bed rest is a time honored procedure which is as important today as in the days before the advent of tuberculostatic drugs. At a recent meeting of the National Tuberculosis Association, two different speakers gave vastly different figures on sputum conversion in patients on para-aminosalicyclic acid and isonicotinic acid hydrazide. The first speaker treated 89 patients on an ambulatory basis from January to December, 1953, and found a sputum conversion rate of 28%. The second speaker quoted figures from a United States Public Health Service study, with patients given the same drugs, but also the usual sanatorium regimen of rest and graduated exercise, and showed that in a group of 160 patients treated for 8 months over 90% became culturally negative. Despite evidence of this type, several large cities with long waiting lists are trying ambulatory therapy. It is granted that some of the cases treated on an ambulatory basis were retreatment cases, and results in these cases are notoriously poor compared with adequately treated virgin cases. One serious objection to ambulatory treatment is the lack of control of treatment schedules. It is difficult, day after day, for months, to remember to take 24 Sodium PAS tablets daily, and to persist, despite gastrointestinal disturbance of greater or lesser degree. The result is the early development of resistance in the tubercle bacillus, and we again have what is tantamount to a retreatment case. Most observers feel that all cases should be hospitalized or treated under similar conditions, until x-ray stability and sputum conversion are obtained. Even the most cooperative patient finds bed rest difficult, and more so when he does not have the company of other patients sharing the same conditions.

It has been pointed out by some workers that collapse therapy and drug therapy operate on contradictory principles. Collapse therapy reduces the blood supply to the part and reduces the amount of oxygen available to the tubercle bacillus, which is a strict aerobe. In this same way, however, it reduces the availability of the circulating drugs. Temporary collapse therapy, or more properly, relaxation therapy, especially since the advent of INH has almost disappeared from the scene. Artificial pneumothorax and pneumoperitoneum were never intended to collapse the lung but only to relax the tissues and, of course, the tissues with most elasticity; in other words, the healthy tissues relaxed readily and the consolidated or fibrotic areas were unable to do so. Nevertheless, certain cavities could be effectively closed by this method. These same cavities can be more rapidly closed with the new drugs, and this can be done without the dangers of collapse therapy. There is no longer the danger of air embolus, of empyema, of thickened pleura,

*Assistant Medical Director, Emily P. Bissell Sanatorium.
Presented at the combined meeting of Wilmington hospitals, St. Francis Hospital, May 25, 1954.

of trapped lung or other dangers attendant on artificial pneumothorax therapy. There is no danger of atrophic diaphragm, as after pneumoperitoneum. It must be remembered, too, that a large percentage of artificial pneumothoraces could not, for technical reasons, be maintained for the 3 or 4 years necessary for adequate cavitary closure. The recent tension cavity closes with astonishing rapidity under drug therapy, and artificial pneumothorax could be a dangerous procedure with this type of cavity. Drugs do not close rigid cavities better than artificial pneumothorax and pneumoperitoneum, but there is a hope that the cavity can be rendered, to all intents and purposes, a cyst or bulla lined by fibrous tissue instead of epithelium, and sterile for tubercle bacilli.

Phrenic nerve operations have practically no place in today's treatment. Phrenic paralysis could not always be obtained, and the so-called temporary phrenic often proved permanent, with up to one-third loss of total respiratory excursion. Pneumoperitoneum could also produce an atrophic diaphragm, with much loss of function.

Permanent collapse (thoracoplasty) is still used as a primary procedure in selected cases, but it is more commonly used as a space-closing procedure following excisional surgery. Thoracoplasty is a more mutilating operation than excisional surgery, as to be adequate, the corresponding transverse processes have to be partially removed. Apicolysis is now frequently used as an adjunct, and this allows the first ribs to be retained to counteract scoliosis and loss of the normal chest shape. Thoracoplasty does not remove the main focus of disease and does not close very rigid cavities, often only altering the shape of these cavities from circular to cigar shaped. Such cavities can, however, later be more readily excised than with primary excisional procedures. Cavitary drainage can also be done before thoracoplasty, or as concomitant procedure.

EXCISIONAL SURGERY

Where drugs do not effect cavitary closure, or where a caseo-necrotic focus is left, excisional surgery is the procedure of choice, provided there is sufficient good lung tissue and the patient is clinically able to stand the procedure. Excisional surgery may comprise pneumonectomy, lobectomy, wedge resections or segmental resections, e.g., the apical posterior segment of the left upper lobe. The procedure should be done while drugs are still effective, and preferably with sputum still negative.

Except for bed rest the use of drugs concerns the practitioner more than any of the foregoing. We still have no bactericidal drug, but we do have several bacteriostatic drugs. These drugs are bacteriostatic in that they diminish to a variable degree, and by different mechanisms, the reproductive power of the organism. It is to be noted that not all colonies may be equally affected, and this possibly explains why a patient can be resistant and yet improve both on x-ray and clinically. On the other hand, where the majority of organisms are being excreted by one or more cavitary lesions, when resistance develops, it is more likely to develop in most or all colonies simultaneously. Cavitary closure is, therefore, the key to successful drug therapy. The Veterans Administration, Army, and Navy use the term "target point" in their discussion of the effect of drugs. By definition, the target point is reached when there is: (1) sputum conversion, (2) cavitary closure, and (3) stable x-rays. If cavitary closure is not obtained by drugs, surgery is resorted to if feasible, and this objective is usually reached in 6 months following the beginning of drug therapy. In less favorable cases the patient may not be brought to surgery for years, and in some cases when surgery is not feasible, the decision has to be made as to whether to continue drugs in the presence of any *open* cavity, and hope that by the time these drugs have exhausted their usefulness, some new drug may be available. Some observers say that drugs should be continued in chronic cases as long as sputum remains negative on culture, and others as long as there is clinical or x-ray response.

DRUG THERAPY

The drugs in most common use are three in number: Streptomycin, (SM); Para-omino-Salicylic acid, (PAS); and Isonicotinic acid Hydrazide, (INH). These drugs are used in various combinations, but it is mandatory that they never be used except in combination. No one drug should ever be used alone.

Streptomycin is the drug best known on this continent, partly because it has uses other than in tuberculosis, and partly because it was first used here before any of the other drugs. SM is used twice a week, or every three days, in doses of 1 gram, and it is never used in greater or more frequent dosage except in very exceptional circumstances, such as tuberculosis meningitis. SM is used in preference to Dihydrostreptomycin for a very good reason. The efficacy of both drugs is about the same, but Dihydrostreptomycin may cause deafness, and this process is somewhat progressive, even after therapy is discontinued, and it is irreversible. SM may cause vertigo, and this again is somewhat progressive, but it can be compensated for by the patient. Used alone in doses of 1 gram daily, there is almost complete resistance in 90 days in a large percentage of cases. The concomitant use of PAS delays the onset of resistance in such dosages. However, if SM is given on an intermittent schedule with daily PAS, the onset of resistance may be delayed for years, on virgin soil.

Para-aminosalicylic Acid. This drug has the advantage that the onset of resistance is slow and usually does not occur in less than one year, even when used alone. Also, the drug is taken orally. There is, however, in a fair percentage of patients, gastro-intestinal intolerance, with nausea and vomiting and/or diarrhea. This is true, especially with cheaper and less pure preparations, and as the freshness of this drug may affect its purity, only new stock should be used. The minimum effective blood levels are obtained with 8 grams daily, and it is to be remembered that *12 grams sodium PAS represent 8.5 grams PAS.* It is usually used in combination with SM, or the latest of the drugs in common use, INH.

Isonicotinic Acid Hydrazide. In 1952 this drug was hailed as the wonder drug, but soon many doubts were raised as to its efficacy because of the early onset of drug resistance. It is given orally, is easily tolerated, has few side effects, has a marked clinical effect in almost all cases, and has a marked x-ray effect in many cases. It differs from the previous drugs in that it enters the cell and acts within the lymphocytes. There is a great deal of controversy at the moment as to whether or not the onset of drug resistance is of any consequence. One school has produced results showing that although numerous organisms may be recovered from cavities on operation, these organisms have been so altered that they are non-pathogenic for guinea pigs, and also, it is presumed, for man. Another school says, "guinea pigs are not men". In any case, there is universal agreement on its efficacy in acute lesions such as early tuberculous bronchopneumonia, where the lesions may be completely reversible; and in early tuberculous meningitis, where the results are dramatic and there is no longer need for intrathecal therapy, as the drug enters the spinal fluid in good concentration and also enters the lymph cells. There is an extremely rapid return to normal cerebral-spinal fluid chemistry. The miliary lung lesions also disappear rapidly, and in 6 to 9 months the x-ray may appear normal. The usual drugs and schedules are 3-5 mgm. per kilo of body weight, and in tuberculous meningitis, 7 mgm. per kilo. Recent observations would tend to show that doses of 8 mgm. per kilo are optimum for any type of disease, and are well tolerated in most cases.

The most common untoward reaction is polyneuritis. INH should not be introduced until an adequate number of sputum specimens have been secured, including gastric washings, as sputum conversion is usually so rapid that otherwise there may never be bacteriological proof that tuberculosis is present. The usual combinations are SM and PAS or SM and INH, where the patient is hospitalized. Combined tab-

lets of PAS and INH are used when the patient is at home and cannot readily secure hypodermic medication. SM and INH appears to be the regime most immediately effective, with SM and PAS for the long haul.

We have used triple therapy, (SM, PAS and INH), as the regime of choice, but studies by the Veterans Administration, etc., show no advantage in this regime, in studies of eight months duration. As the only purpose of using triple therapy is to delay the onset of any resistance, eight months proves nothing, and we shall not know for two or three more years if this is the regime of choice in virgin cases. In cases who have previously received one or more of these drugs, triple therapy is more commonly used, particularly pending resistance studies. It is known that when two drugs are in use, if resistance develops to one of the drugs, it usually develops to both simultaneously. My feeling is that it must take longer for the organism to develop resistance to three different drugs than to any two drugs, because if the organism becomes resistant to any one drug it still has combined therapy to overcome, and there is no controversy over the delay in development of resistance where two drugs are used in preference initially. A good working policy is to treat with two drugs patients who are likely to reach the target point in one year or less, and to give triple therapy where longer term therapy is likely to be used. The only other drug we use at all extensively is Viomycin and it is used in much the same way as SM, but in doses of 2 gms. We use it where resistance to SM has developed and never as one of the original treatment drugs.

Terramycin is said to delay the onset of resistance to SM and for this reason is useful where antibiotics are necessary for non-tuberculous complications.

Pyrazinamide, according to some observers, can replace PAS, but most observers consider it too toxic for the liver, and its duration of efficacy too short.

Tibione is also considered inferior to PAS and much more toxic.

DRUG INTOLERANCE AND HYPERSENSITIVITY

When using drug therapy, a constant lookout has to be maintained for drug reactions, which are protean in nature, and which increase in number as the number of drugs used increases. The commonest of all the reactions are gastric intestinal intolerances from PAS, vertigo from dihydrostreptomycin, deafness from SM, and polyneuritis from INH. Gastrointestinal intolerance is the easiest to recognize, and is the most dramatic as far as the patient is concerned, as cause and effect are so obvious. Vertigo is also usually easily recognized as, when it is developing, the patient complains of dizziness or perhaps of nausea after each injection, and remains well until his next injection.

Deafness is most insidious and must be carefully guarded against, especially in young children being treated for meningitis.

Drug rashes are not uncommon, particularly with PAS or multiple drug therapy, and may be sufficiently severe to justify temporary withdrawal of all drug therapy.

High fever may not be recognized as due to the drugs, but a good clue is the height of the fever—usually 103° to 104° in a patient, who previously had little or no fever.

Where, occasionally, a fourth drug, such as Terramycin has to be used for intercurrent infection, it is better to withdraw one or two of the tuberculostatic drugs, and as terramycin is said to delay the onset of resistance to SM, we are in the habit of withdrawing PAS and substituting terramycin for the necessary period. On several occasions where multiple drugs have been used we have noted symptoms of mental confusion, which cleared up spontaneously when all the drugs were withdrawn and did not reappear when a lesser number of drugs was used.

INH often causes some degree of euphoria, but it may also, in a small percentage of cases, cause confusion and disorientation. Polyneuritis is the most usual and most severe of the side reactions due

to INH, and we are very careful to treat any avitaminosis, particularly in alcoholics. It is thought that INH interferes with the utilization of vitamin B6.

A tendency to bleed is not uncommon, particularly with PAS, and we find prolonged prothrombin time in most of these individuals. Vitamin K seems to be effective in controlling this complication.

Where drug intolerance has manifested itself we usually withdraw all antimicrobials and reintroduce them one at a time. If PAS hypersensitivity is present a trial dose of 0.5 gm. will produce hyperpyrexia, which will disappear in a few hours after the drug is discontinued. Once the offending drug is known, desensitization is carried out.

THE SURGERY OF PULMONARY TUBERCULOSIS

FRANK T. O'BRIEN, M.D.,*
Wilmington, Del.

Since DeCérenville of Lausanne, Switzerland, (1885) performed the first thoracoplasty to relax the rigid chest wall over a tuberculous lesion, surgery of this disease has advanced in geometric progression. The trial and error techniques are being gradually supplanted by scientific evaluation and physiological reasoning. We owe ever so much to the early pioneers as mentioned in the late John Alexander's book. Their experiences and failures, combined with anti-tuberculous drugs, better anesthesia, and a host of research, have produced a new era in the treatment of the "white plague". It has become a surgical disease in great measure.

The sanatorium has emerged from a nursing home to a hospital for chest diseases, where active methods of therapy are extensively applied. Having been diagnosed as having pulmonary tuberculosis, the patient should be given the benefit of sanatorium care. Here he will receive instructions as to the nature of the disease. He will see the effectiveness of antibiotics on the old chronic and the recent pneumonitics. The education is invaluable. Here, too, he will be placed on a definite plan of therapy. Adequate diet, bed rest, and properly scheduled medication will become a ritual of which he will indelibly be a part. His mental attitude must be healthy; therefore, agencies must take the burden of his commitments in the outside world until he is able to resume his rightful place in society.

The acute and sub-acute cases have to be "cooled off". Thus bed-rest, streptomycin, para-aminosalicylic acid, isoniazid, and adequate diet have, in many cases, produced a cure. That is, the patient overcomes the pneumonitic infiltration completely by the natural healing process of resolution and fibrosis. It is when the resolution is incomplete due to mechanical, anatomical, physiological, or pharmacological failure that surgical help becomes a necessity. An irreversible pathological change in the lung parenchyma as seen on x-ray, initiates the subsequent intervention.

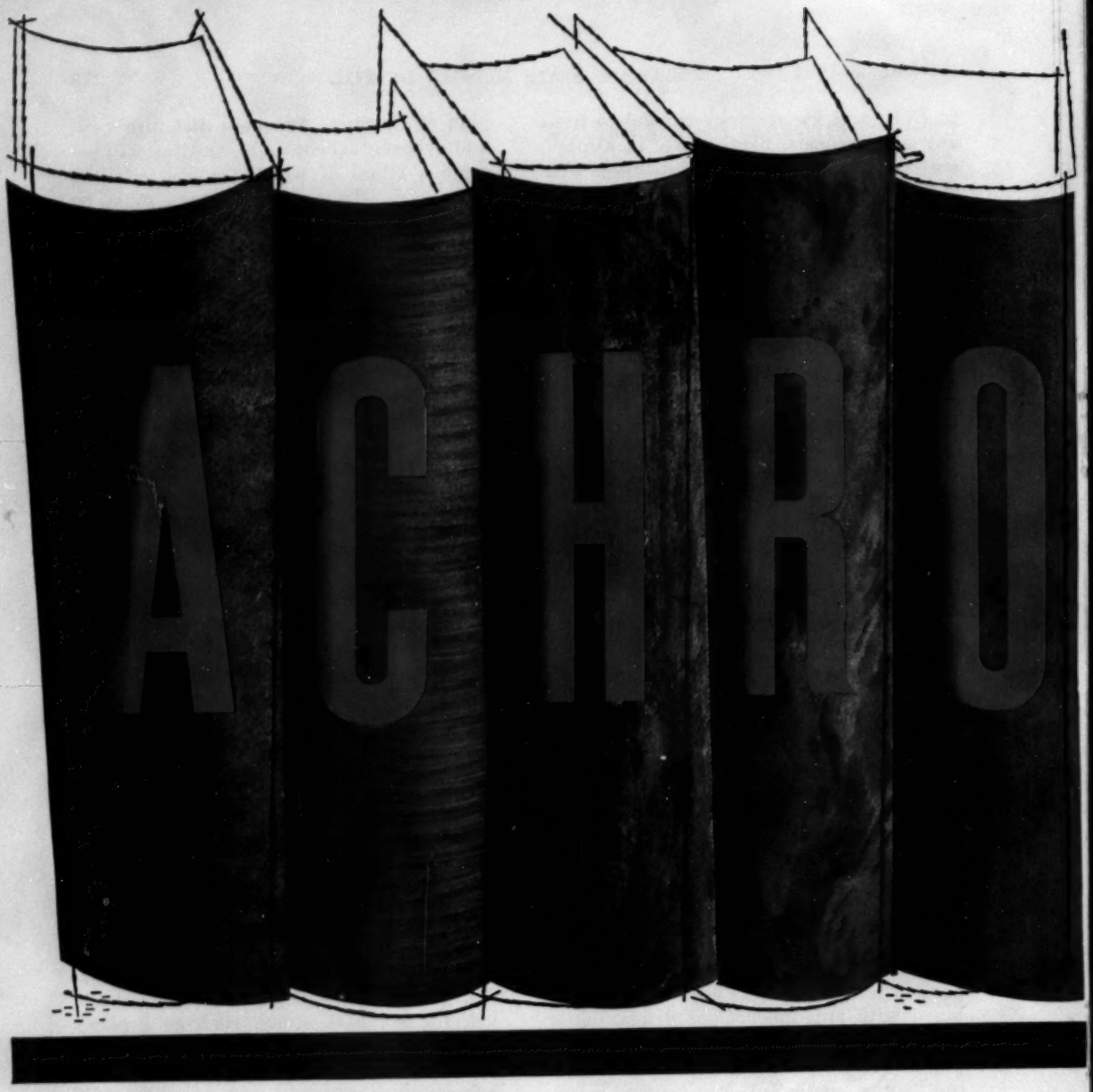
Selection of cases is done with utmost care, as a mortality, even on a calculated risk, may dissuade the salvage and rehabilitation of several patients who are waiting for the optimum effect of their preoperative therapy.

The clinical history is carefully reviewed, the laboratory data and x-rays gone over again and again. The ward physician confirms the mental attitude, outlook, temperament, and general adjustment of the patient. Frequently, the phthisiologist, roentgenologist, or surgeon will ask for a repeat study, such as a plano gram, bronchogram, bronchoscopy, sedimentation rate, sputum, gastric or urine examination before he will give his opinion. It is rare that a case is selected for surgery after one presentation to the combined staff conference. Opinions usually vary; yet complete accord is reached before a definite procedure is carried out. This screening is followed on admission and whenever a change in the patient's program is deemed advisable. Thus, a patient may be presented weekly, monthly, or at eight week intervals.

The surgical procedures that are recommended fall into three general categories:

(Continued on page 283)

*Visiting Thoracic Surgeon, St. Francis Hospital.
Presented at the combined meeting of Wilmington hospitals, St. Francis Hospital, May 25, 1954.



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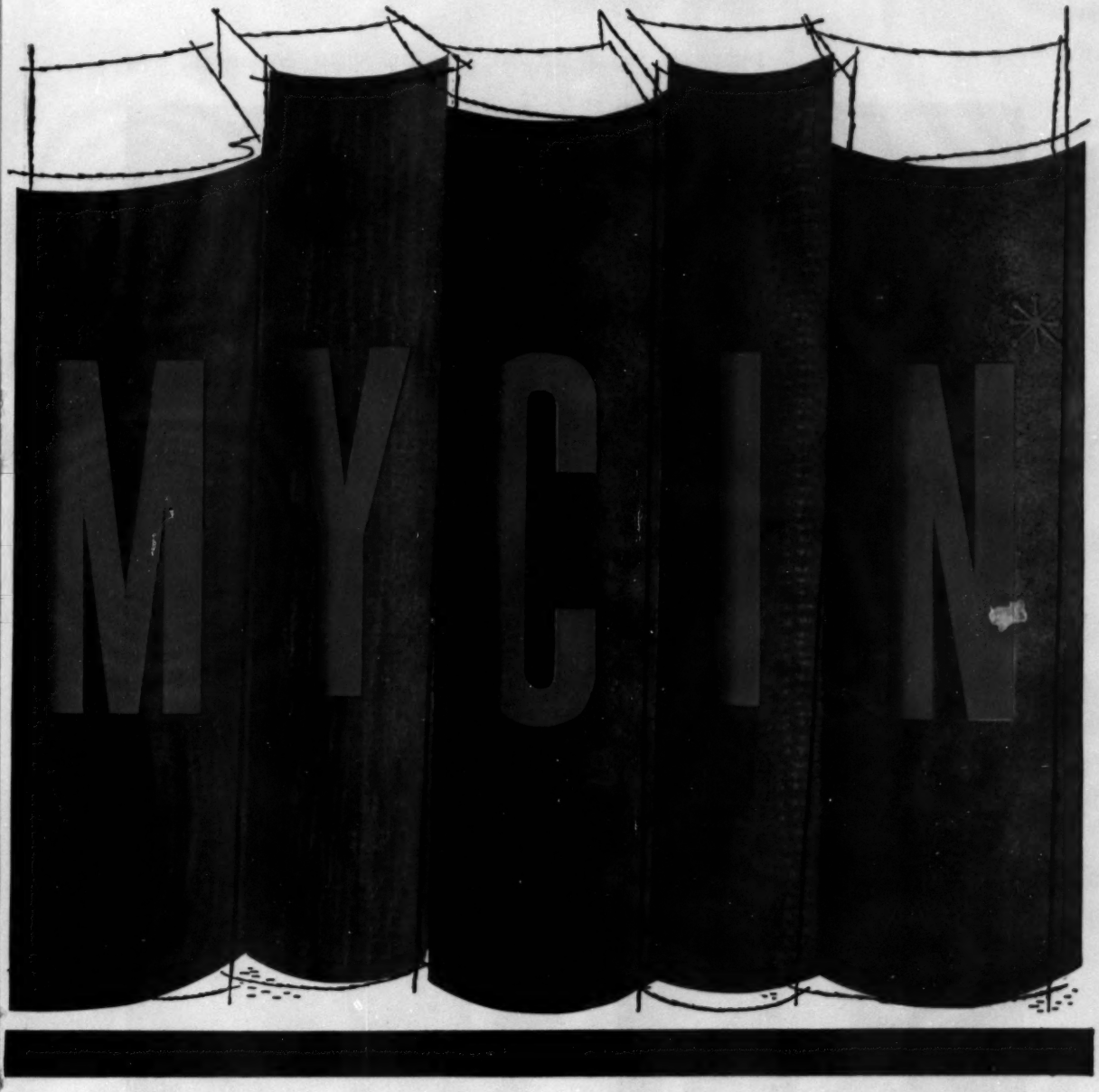

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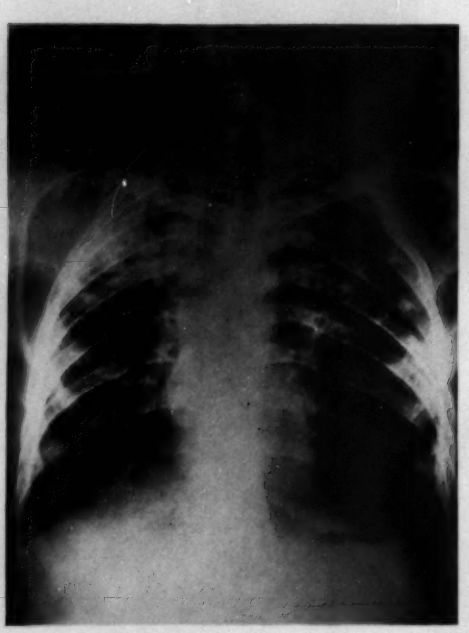
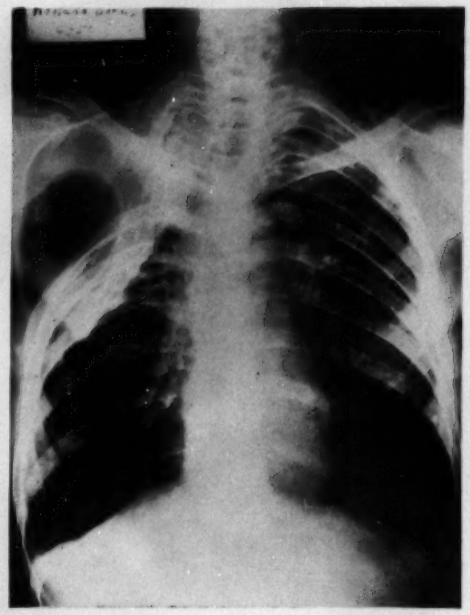




a Preoperative

*FIG. 1

b Postoperative

B. H. 58 year old colored male.
following a small one stage thoracoplasty and semi apicalysis.

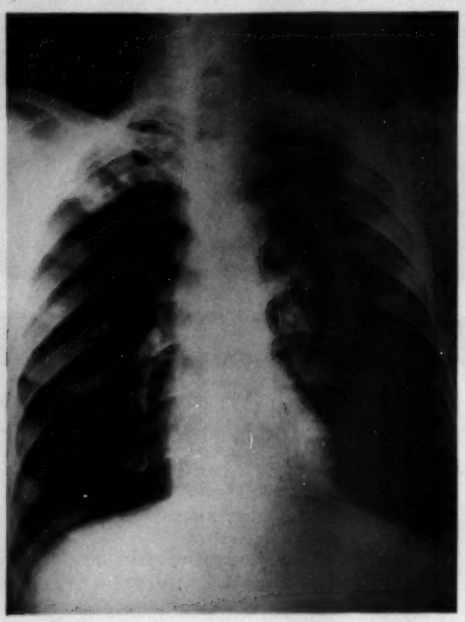


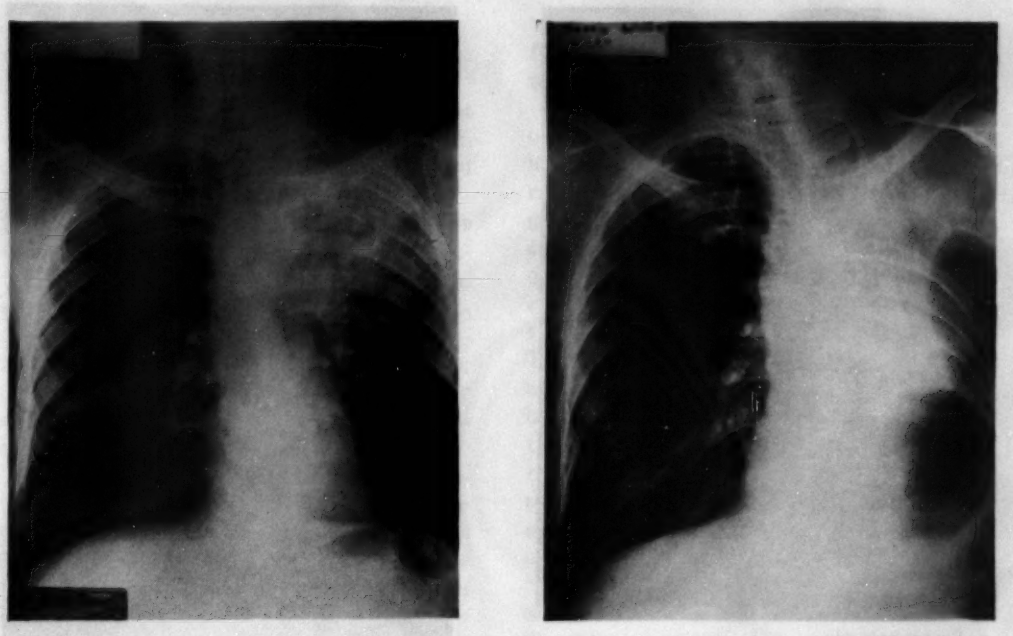
FIG. 2

D. H. 45 year old white male.

a P. A. film, showing lesion in right upper lobe.

b Planogram of right upper lobe. Lesion removed by segmental resection thoracoplasty not necessary.

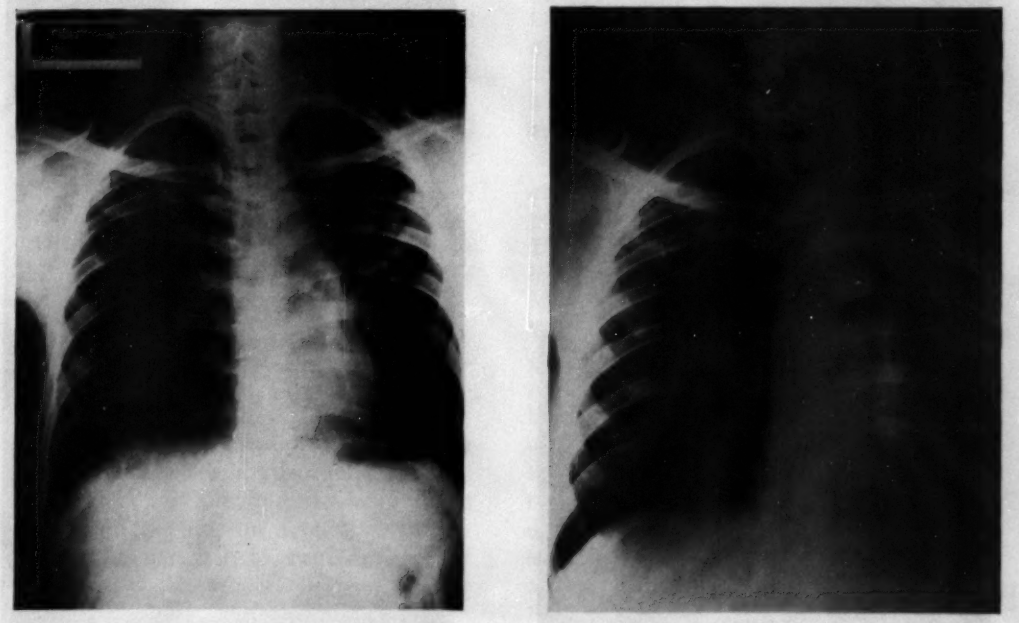
*Patients from the Emily P. Bissell Sanatorium.
Operations performed and slides prepared at The Delaware Hospital, Wilmington, Del.



a Preoperative FIG. 3 b Postoperative

W. H. a 40 year old colored male.

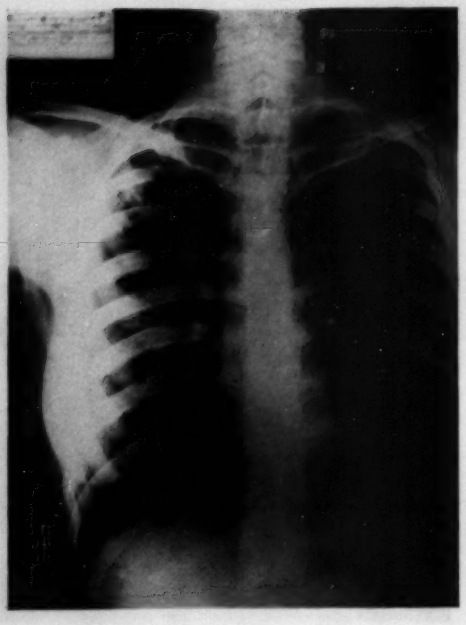
A pneumonectomy was performed because of the disease found in the lower lobe. Postoperative film shows very little mediastinal shift due to the small thoracoplasty and the left phrenic resection.



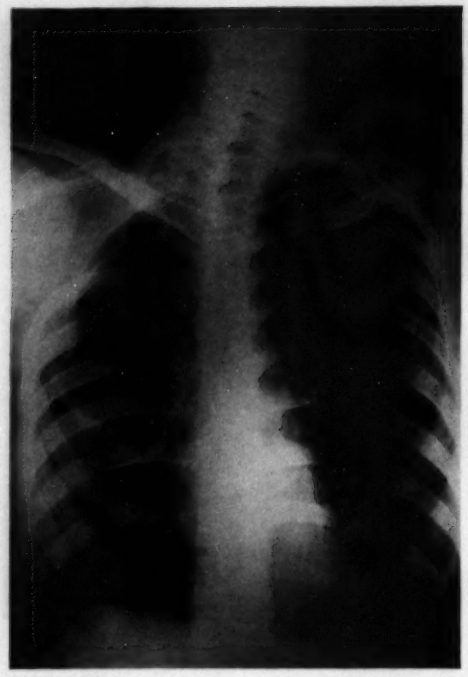
a Preoperatively FIG. 5 b Postoperatively

E. S. a 27 year old colored male.

following left upper lobectomy and tailoring thoracoplasty.



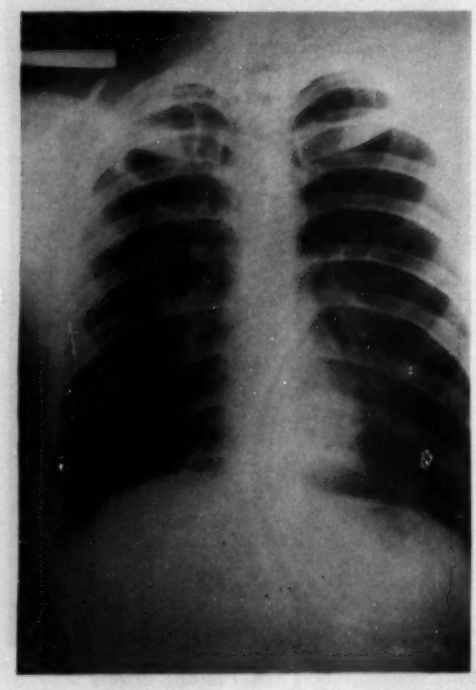
a Preoperatively



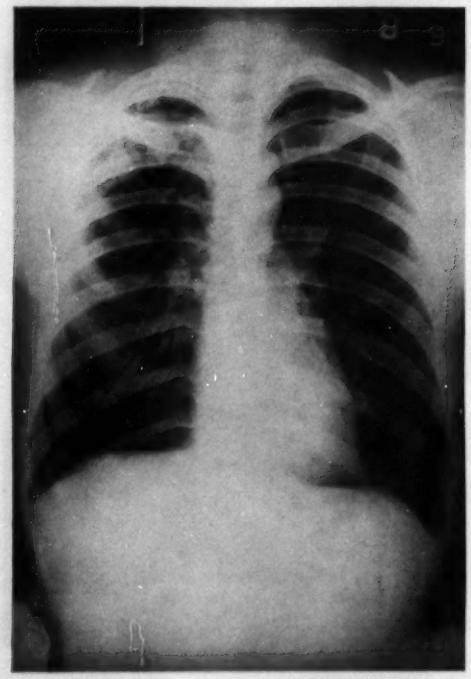
b Postoperatively

FIG. 4

Two right upper lobectomies, the first with thoracoplasty.



c Preoperatively



d Postoperatively

The second without thoracoplasty (the lower and middle lobe easily filled the right pleural space.)

THE SURGERY OF PULMONARY TUBERCULOSIS

(Continued from page 279)

(1) reversible collapse; (2) permanent collapse; (3) resection. Due to the frequency of complications, the decreased pulmonary function, and the technical difficulties, many of the former collapse methods have been abandoned. The effectiveness of the drugs has also helped to alter the former concept of these procedures. We seldom use pneumothorax, pneumoperitoneum, plombage, or phreniclasia; and the thoracoplasty is used primarily as a pre-resection or a post-resection procedure.

It has been estimated that pneumothorax and pneumoperitoneum decrease the respiratory function by 30%. A thoracoplasty or interruption of the phrenic nerve decreases the respiratory function by 10-15%. Pneumothorax and pneumoperitoneum have virtually been abandoned. We occasionally crush the phrenic nerve after a pneumonectomy or in elderly patients who have controlled their disease but whom we feel need a little protection to prevent a reactivation. The former criteria for a thoracoplasty are now used for excisional surgery. We have adopted the British plan of thoracoplasty, reserving it for:

1. Patients over age 40 preparing for resection.
2. Patients with bilateral apical cavitory lesions.
3. Patients whose tubercle bacilli have become resistant to the drugs and have persistent cavitations.
4. Post-operatively, after a resection, to prevent over-expansion of the remaining pulmonary tissue, a tailoring thoracoplasty is performed.

The tailoring thoracoplasty which is usually done incorporates dividing Sibleau's bands and allowing the dome of the pleura and periosteum from the underside of the first rib to approximate the mediastinum and descend toward the hilum of the lung. The slide shows the result of a one stage thoracoplasty with Semb apicalysis on an elderly patient (Fig. 1.). This patient converted his sputum and made a spectacular recovery following this meager surgical help. Many patients are not as fortunate.

Direct attack on the persistent reservoir of the tubercle bacilli by pneumonectomy, lobectomy, segmental resection, or wedge resection has become the most used surgical procedure. Credit for the first resection was given to Sir William McEwen, of Glasgow, in 1906, but the advancement of the techniques is due to contemporary surgeons: Churchill, Overholt, Blades, etc. These changes again were due to better anesthesia and the sensitivity of the tubercle bacilli to antibiotics. Even up to the series of Thornton and Adams in 1942, resections were reserved for gravely ill patients. Thus, cavernostomy was widely used until 12 years ago; now it is rarely used. In bad risk patients, before the use of streptomycin, the mortality rate was about 35%, making resection a very dubious surgical aid. Up to 1944-45, Overholt reported 196 resections with 46 deaths, a mortality rate of 24%. The advent of streptomycin, the substitution of meticulous hilar dissection for the old tourniquet method of resection, and the attention paid to pulmonary function have greatly reduced morbidity and mortality. In Great Britain, Edwards in 1952, had a mortality rate of 2.5% in over 200 resections.

With careful selection of cases and operating when the patient is at the "target point", an uneventful recovery is usual. The small lesions which are left behind, in order to preserve pulmonary tissue, must have a stable appearance on x-ray. The ideal case for resection is the filled cavity or tuberculoma which represents massive nodular disease. These lesions can be "watched" too long. Not only do they often break down, but they may mask malignancy. X-ray evidence of calcified center, round edges and other diagnostic radiologic signs of a healed lesion, is not always true. The slide shows planograms of a so-called healed lesion as well as the P.A. film (Fig. 2). This lesion had two cavities and the purulent centers smeared positive for acid fast bacilli. It was easily removed by a segmental resection under

the protection of streptomycin. The patient is now virtually cured and will not live in fear of the lesion breaking down. We have resected three cases in the past three years which were diagnosed as tuberculomas but proved to be bronchogenic carcinomas. Of course, the reverse has been true more frequently, but this does not justify failure to perform a thoracotomy for a round lesion, or undiagnosed, doubtful pulmonary shadow.

A destroyed, functionless lung should be resected both to get rid of the dead space and to remove the possibility of the inevitable secondary infection. After adequate antibiotics, (but while they are still effective), a lower lobe cavity or tuberculous bronchiectasis should be excised. Indications for resection are therefore as follows:

1. Gross unilateral disease.
2. Lobar bronchiectasis.
3. Caseous mass.
4. Cavities:
   a.) Cavities which fail to close and are confined to one lobe or segment.
   b.) Lower lobe cavities.
   c.) Emergency for ruptured cavities causing either hemorrhage or pneumothorax.
5. Thoracoplasty failure.

Slides 3, 4, and 5 show the pre-operative and post-operative x-rays of a pneumonectomy, right upper lobectomy, and left upper lobectomy. They have all been performed here in Delaware and these patients are now rehabilitated. The deformity with a small thoracoplasty is so minimal it cannot be noticed due to the scapula in the back and the pectoral muscles anteriorly. The psychological effect on the patient who knows that the disease has been removed or rather that the main focus has been extirpated is beyond compare. The concomitant thoracoplasty is performed in all cases where a large volume of lung tissue is removed or where known disease has existed in so-called good lung. The prevention of overdistension of healed (fibrosed) pulmonary tissue is worth while, and, as many patients dread or refuse a second operation, we perform both at the same time.

Post-operatively the patient is urged to cough and if tracheal aspiration fails to prevent atelectasis he is bronchoscoped in bed. Two drainage tubes are used. These are right-angle catheters that will hug the chest wall yet drain the apex and costo-phrenic angle. Usually underwater drainage is all that is necessary. If, however, a segmental resection or decortication is followed by airlleaks, a Stedman pump may be used to keep a negative intra-pleural pressure (removing the air faster than it leaks from the alveoli). The lower tube is removed on the third day, the upper tube on the fifth postoperative day. The patient is usually out of bed on the second day, sutures removed on the seventh or eighth day, and he returns to the sanatorium on the twelfth day. He is then placed on the postoperative routine of bed rest with antibiotics for six months. During this six months his case may be presented to the conference on several occasions, especially if his classification is to be changed. When his medical discharge has been ultimately approved, his home conditions must be cleared by the social service department before he is allowed to leave the sanatorium.

Surgery of pulmonary tuberculosis has greatly advanced in the past ten years, and it will always play a major role in helping selected cases. Good results depend on the whole team: family doctor, roentgenologist, bacteriologist, nurses, dietitians, social worker, chaplain, other patients, phthisiologist, and surgeon. The patient who understands and respects his disease will spend the necessary time in the sanatorium; will reach the "target point"; will be operated on; will give a full six months to convalescing, and will be one of the 90% of cases who can be rehabilitated.

Our statistics will be presented at a later date, but in twelve months, we completed about fifty cases—60% resections, 20% thoracoplasties, and 20% miscellaneous (cavernostomies, phreniclasias, etc.). We had three deaths, one a cavernostomy on the eighth post-operative day, one

thoracoplasty (the patient had an interventricular septal defect) on the seventh post-operative day, and one lobectomy who died on the sixth post-operative day. The deaths were all on poor risk patients who were operated on as a last resort.

We have not discussed particular operations or techniques, but have attempted to show the overall picture of the surgery performed here for pulmonary tuberculosis.

DIABETES MELLITUS IN JUVENILE IDENTICAL TWINS

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Wilmington, Del.

INTRODUCTION

"There is very little difference between one man and another, but what little there is, is very important."[1] The difference becomes even less marked when identical twins are born into the world. Newman[2] has set up criteria for the identification of monozygotic twins, and what little difference there is becomes increasingly important in telling them apart. Their hair, eyes, complexion, and teeth, must be the same in most respects. Similarity of appearance and finger prints are also stressed by him to be the two most reliable means of identification.

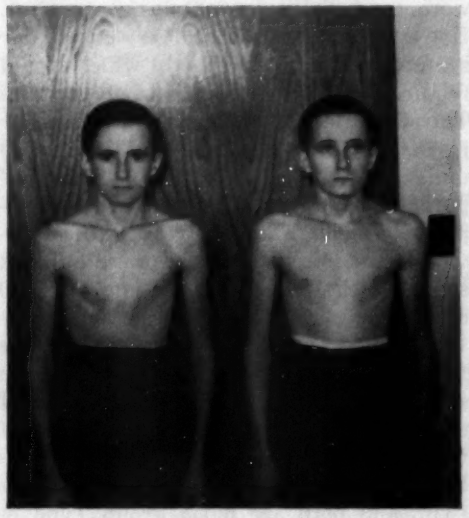

FIG. 1
John (left) and Joseph, twin diabetics.

*Chief, Department of Metabolism, St. Francis Hospital.

The twins in our study meet these qualifications, and, in addition, they developed diabetes mellitus at approximately the same time. From the standpoint of research in heredity, these 15 year old twins with diabetes give us an exceptional opportunity to study: (1) the effect of environmental influence on a disease which is subject to Mendel's laws of genetics; (2) the variance in the course of the metabolic disorder which is known to occur in other twin diseases; (3) the careful observance of the diabetes in its juvenile form in both patients, which can be a study in itself.

Galton,[3] in 1883, stated that illness and accidents were the only causes which appeared to be adequate in making identical twins unlike. Identical twins are not obliged to have the same diseases, although the tendency is strong to do so, nor are they necessarily subject to the same course of any disease which they may develop.

Newman et al[4] verified this statement of Galton's, and concluded that the nature and course of the malady occurring in identical twins is often not identical. Newman[5] spent a quarter of a century in twin research. He coined the term "literary twins" to describe the liberties taken in books and plays with the subject of twinning. Describing Shakespeare's experience with Olivia and Sebastian in "Twelfth Night", he says "one might infer from Shakespeare, who, in error or with poetic license, invented one-egg twins in his famous 'Twelfth Night', that identical twins could be of opposite sex."

CASE REPORT OF TWIN NO. 1

Joseph was the first to manifest symptoms and signs of the disease. On April 24, 1953 he was admitted to St. Francis Hospital complaining of thirst, hunger, and polyuria. He had lost 11 pounds in the past six weeks. His physical examination was normal for a boy of 15 years, and included an eye-ground examination which was negative for diabetic disease. The

blood count was within normal limits, and so was the blood pressure. CO_2 combining power was 54 volumes per cent. Plasma acetone was also negative. His blood sugar on admission, taken two hours after breakfast, was 315 mg. per 100 cc. of blood. Urinalysis was 4+ for sugar, and negative for albumen.

A diet was prescribed and the patient was placed on 25 units of globin insulin at breakfast time. He was followed in the Diabetic Clinic at the hospital and the insulin dose adjusted to 28 units of globin in the A.M. and 12 units at supper time. This twin's weight rapidly increased, and he became symptom free. No urinalyses were done as a routine guide for therapy. The therapy was carried out entirely according to the compatible hyperglycemia method of control of Anthony Sindoni,[6] consultant on metabolic disease at the hospital. Blood sugars were taken weekly until the boy was stabilized without symptoms, free of acetonemia and acetonuria, and running a two hour post-prandial sugar level of approximately 250 mg. per 100 cc. of blood. Since his discharge from the hospital he has had a weight gain of 17 pounds in 18 months. He feels well on his present dose of insulin, and is symptom free of diabetes mellitus. In July, 1954 a basal metabolism rate was found to be +4. 17-ketosteroid excretion in 24 hours was 12.4 mg. Blood cholesterol was 261 mg. per 100 cc. of blood. X-ray of the sella turcica was negative. The boy is happy, well adjusted, and is a good student in high school.

His diet is 120 Protein + 80 Fat + 220 CH + 30 CH at night. His post-prandial blood sugars have averaged about 240 mg. per 100 cc. of blood since discharge from the hospital in April, 1953. The other twin is on the same diet.

CASE REPORT OF TWIN NO. 2

John was admitted to the Diabetic Clinic at St. Francis Hospital in July, 1953 for study of his carborhydrate metabolism. A fasting sugar of 165 mg. per 100 cc. of blood was obtained. His urinalysis was negative for sugar. It was decided to follow this twin, although he did not complain of diabetic symptoms. Another sugar was done two hours after breakfast. This post-prandial reading was 145 mg. Since there was still a doubt as to the diagnosis, an Exton-Rose glucose tolerance test was done. It read 130 mg. fasting, 214 mg. on the next reading, and 220 mg. on the last reading. Only the one hour urinalysis was positive for sugar. The weight gain has been 15 pounds since admission to the diabetic clinic.

An X-ray was taken of the sella turcica: no abnormality was demonstrated. Basal metabolism rate was — 2. Blood cholesterol was 219 mg. 17-ketosteroid excretion in 24 hours was 22.2 mg. per 100 cc. of blood. X-ray of heart and lungs was normal. The eye grounds were perfectly normal for his age. Wassermann and Kahn were negative in both twins. No insulin was used until October, 1954.

The subsequent course of the disease was of a mild nature. No symptoms or signs of uncontrolled diabetes developed. The blood sugar varied from 116 mg. post-prandially to 187 mg. in September, 1953. No sugar values over 200 mg. were reached by this method of control until February, 1954, when 212 mg. was obtained, two hours p.c. Since then, readings of 214, 195, and, in September of this year, 242 mg. per 100 cc. of blood were reached in a symptom-free patient. However, he was watched very closely for symptoms of lack of control which would require the administration of insulin. Thirst and loss of weight began to appear in October, 1954, and he was put on 10 units of globin insulin daily. The boys' parents claim that the twins are exemplary patients, and follow all medical advice to the letter. The post-prandial blood sugar on the mother was 90 mg. per 100 cc. of blood. The father's blood sugar was 112 mg. 2 hours post-prandially. The father's brother developed diabetes in the summer of 1954; there was no history of any other diabetic disease in the rest of the family for two generations. John's intelligence in school is identical with his twin, and both are blood group Type A, Rh positive. Their fingerprints are somewhat similar but of course not identical.

The similarity meets Newman's[2] criteria for fingerprint identification of identical twins.

SIMILAR TWINS

The study of identical twins is fascinating and often humorous. Ora and Ira[7] were in business in Jefferson City, Mo. The law arrested Ora, who stepped into a back room and sent Ira out to go with the police. At the station, Ira told the police he was not Ora, but they did not believe him. Ira was convicted in Circuit Court. The Supreme Court let him go because he could not be charged for the offense; he only worked for Ora.

Recently, identical twins were brought into the world by identical twins.[8] Passports have been substituted without detection and identical twins have played on the same football team, confusing the other team to a distressing degree.

Alvarez[9] says that twins pose special behavior problems, claiming the mother must be careful to give both twins exactly the same amount of attention and love. He reports twins early adopted and living apart. Their interests were, nevertheless, alike. Both were athletes and prize-fighters, although at the time neither knew the other existed. Galton, according to Alvarez, says identical twins often die within a few weeks of each other.

The case of Millar and George[10] is a classical one of identical twins reared apart, after being separated at birth. When re-united at 18 years of age, each had like personality tests and a weakness in mathematics and word meanings. In almost all cases where a cavity was noted in one boy's tooth, the corresponding tooth of the other was also affected.

Twins[11] living 1,000 miles apart and not known to each other worked for the same telephone company. Each had a terrier dog with the same name, "Trixie". They were discovered by a third person working for the same company.

Identical twins were separated at birth in Switzerland.[12] A single birth was sent home from the hospital with one twin. Fortunately, the three children were brought up in the same town, and after seven years the misplaced similar twin was identified as a double to one of the two children reared as fraternal twins. Suspicion was then aroused that the three babies had been mixed up in the hospital. Eventually the following similarities were noted. Phillipe had only two incisors in his lower jaw instead of four. Ernstle had the same number. The children were studied for two weeks at a medical clinic, and the pattern of the retina of the eyes was identical, left to left, and right to right. The irises of the left eyes were more similar to each other than to their own right eyes. Both were color blind. Skin grafts took immediately on the real twins, but were sluggish and crusty on the mistaken twin. X-ray plates of their left hands showed three missing carpal bones in each case. After the children were together for a while they were both found sucking the right thumb.

The incidence of identical twins is 25% of twin births, which occur 1 in 87 total births. One often wonders why many hundreds of births go on in some hospitals before twins are born. The reason may be that twinning families live in the same town, or neighborhood. Twins beget twins. In Delmar, near Wilmington, three sets of twins were born in August, 1954, at the Peninsula General Hospital. In September, 1954, in Overlook Hospital in Summit, N. J., the birth of three sets of of twins in an 18-hour period was reported in the *Journal-Every Evening*, the Wilmington evening newspaper.

Identical twins have as differences only those traits developed due to environment. They are always of the same sex and complexion. Their eyes are of the same color, as is their hair, and blood type. They usually develop to the same height and build. Some differences appearing before as well as after birth can be traced to environment. Newman, Freeman, and Holzinger[13] studied twins reared together and reared apart, and found little difference except that due to environment. Height was less affected than weight, which is modified more easily. This does not mean that weight is not subject to hereditary influence. Newman describes another interest-

ing observation about identical twins. One had a criminal record and the other was also in prison. They were living far apart from each other.

Battista[14] supplies us with the following information about twins: "There are 3,000,000 in the United States; 800,000 are identical. Cases are on record in which the mothers have made the mistake of feeding the same child twice, only to be bewildered by the uncompromising behavior of the neglected and very hungry child.

"On the basis of hereditary studies, the fathers' hereditary background appears to determine the arrival of identical twins, whereas the mothers' hereditary history influences the arrival of fraternal twins. Identical twins think of themselves as a unit and feel incomplete when separated. They often marry and have children at the same time. Simultaneous thoughts or statements often occur."

DIABETES MELLITUS IN TWINS

Diabetes is but one of many diseases occurring in twins.[15,26,17] Any disease is more likely to occur concurrently in similar than in dissimilar twins. Similar twins are monozygotic. They have a tendency to be identical in the shaping of their lives, both as to vocation and disease. Uniovular twins have been reported with concordant multiple sclerosis.[15] Severe megaloblastic anemia[16] was reported in girl twins 10 months old. Duodenal ulcer[17] occurred simultaneously in twin brothers. Carcinoma of the cervix uteri[18] in identical twins was reported by Stocking in 1950. Tuberculosis in identical twins in calcified mesenteric glands was found on x-ray by Hoffstaedt.[19] Their mother had active tuberculous disease of the lungs.

Diseases have a tendency to occur simultaneously in identical twins. Terry,[20] quoting White, says that the onset of diabetes was almost simultaneous in 10 out of 15 identical twins. In the other 5 pairs, there was an interval of 5 to 30 years. In reporting 13 cases, Curtis[21] found that 12 had been reported with diabetes until 1929. His report made the 13th. 10 of the 13 were similar twins, two dissimilar and one pair doubtful. Peck[22] reported a case, and mentioned 18 others in 1933. By 1933, 20 cases of diabetes were reported in the medical literature, and Watson[23] added another. In 1948, Terry[20] reported identical Negro twins with diabetes mellitus.

Fischer[24] had one identical twin with diabetes at the age of three years and nine months, following an attack of measles. Her twin sister had measles at the same time, but did not develop the disease. They were given the same diet for psychological reasons. 16 out of 33 sets of similar twins, analyzed by Joslin[25] were diabetic. Dissimilar twins were diabetic in the ratio of 2 out of 63 pairs. Five case histories of otosclerosis in identical twins have been reported by Fowler.[26]

HEREDITY AND ENVIRONMENT

It is known[27] that many of our human characteristics, such as the color of our eyes and the character of our blood are hereditary in origin. Other traits, as language and religion, are products of our environment.

We inherit our natures about equally from both parents. However, brothers and sisters have different genes, and respond in different ways to an identical environment. Traits determined by heredity may be modified by environmental influences, but these modifications are not passed on to succeeding generations.

We cannot consider the science of heredity without the factor environment which influences it. It is also a fact that all biological species, including man, which reproduce sexually, endow each offspring with a different hereditary make-up. Only identical twins receive the same genes. Genes are passed out to the offspring of all species according to the law of Gregor Mendel, who published his findings on the cross-breeding of peas in an obscure medical journal in 1865. It was re-discovered 34 years later, and the science of genetics was born.

Groups of people resemble each other because they have some genes in common. Most genes stand for useful qualities, but some stand for bad ones, and even diseases. The number of gene combinations is

enormous, each individual carrying several thousand or more. Many people who inherit the gene of diabetic heredity do not develop the disease. The environment must be favorable for the soil.[28] Theoretic genetic ratios are incapable of fulfillment.[29] Environments can be created for the prevention or even the apparent cure of diabetes[30] or other diseases. This is the foundation of the modern day prevention and cure of disease. The doctor can create an environment which may change the course of not only a disease, but of a person's whole existence. Foreknowledge of a hereditary tendency to a disease may be an invaluable aid to the physician in preventing its development, arresting its progress or effecting a cure.[31] Diabetes mellitus is a disease that is similar to gout in the environmental influences on its heredity. As Tweedie [32] stated in the 18th century, "The gout in many instances is hereditary, but it commonly arises from luxury and indolence".

Physical traits such as body length seem to be influenced to a lesser extent by environmental factors. In the case of twins, about half[33,34] the variance is due to heredity, approximately half to segregation,* and little to environment.[35]

HEREDITY AND DIABETES MELLITUS

Diabetes mellitus is a recessive Mendelian trait,[36] and tends to breed out of the family rather than to multiply. Each parent must contribute a recessive gene. Two recessive genes[37] are required to produce the soil for the development of the disease. This is in contrast to diabetes insipidus[38] which traces its heredity to one dominant gene.

The hereditary factor in diabetes mellitus, if capable of true fulfillment, would breed 100% diabetic children from two diabetic parents. If the mother or father alone has diabetes and the mate is not a carrier or potential diabetic, the child will be a carrier, but not a diabetic. Two carriers will breed 25% diabetics in the offspring. A diabetic marrying a carrier will breed out 50% diabetics.

White[39] says that diabetic children who have had diabetes 20 years or longer report the incidence of heredity as high as 60%. Harris[40] studying over 1,200 diabetics also found this to be true. Glucose tolerance tests reported by Sherill[41] on 38 offspring of 23 diabetics were abnormal in 55.3% of cases. Cammidge[42] found a positive family history in 396 out of 1,000 diabetics.

At St. Francis Hospital we are now making an effort to contact and analyze the post-prandial blood sugar in all relatives of diabetics. These people are more interested in the disease than the general population and are more willing to cooperate in any diabetic detection program. The post-prandial blood sugar is 11% more diagnostic of the disease than the fasting blood sugar,[43,44,45,46] and a better index of carbohydrate tolerance in the treatment of the disease. The value of the post-prandial[47] blood sugar and compatible hyperglycemic control of diabetes mellitus is now being appreciated eight years after Sindoni's original work on the subject was published. This acceptance is rapid in comparison to some other discoveries in medicine, as Mendel's law of genes** and Semmelweis, views on childbed fever.

CAN THE LIFE EXPECTANCY OF JUVENILE DIABETICS BE PROLONGED?

The life expectancy of children who contact diabetes during the age group 10-19 years is an average of 16.7 years from onset.[48] This figure can be improved by employing more preventive care. Nutrition should be as good or even better than that of the average child, because of the faulty metabolism. Insulin is required in all juvenile diabetics. Duncan[49] says "all diabetic children and thin diabetics require insulin to grow or gain weight". White[50] says "all children need insulin". One of our twins has only recently taken insulin. His diabetes was probably still in the latent stage when discovered. It is interesting to note that he maintained identical nutrition with his twin, who is on both diet and insulin, until October 1, 1954, when he developed slight thirst and definite loss of weight. His blood sugar shot up suddenly to 290 mg. per 100 cc. of blood and he was losing an increasing

* Matings which produce definite ratios of certain hereditary factors, e.g., albinism (lack of pigment in hair, eyes, and skin).

** First published in Journal of the Society of Naturalists in 1866: cited by Dunn, L. C. and Dobzhansky, T.: Heredity, Race and Society, 42, 1954.

amount of sugar in the urine. When Figure 1 photograph was taken twin John (left) had just begun to lose weight.

Prevention of accidents in our diabetic children is as important as in the non-diabetic children and will prolong their lives. Accidental death in children is three times more common than death from heart disease, and five times more so than from poliomyelitis.[51] The percentage of death from accidents in the age group from 1 to 9 years is about 35% (1953) as compared with 10% in the years 1930 to 1934.

Adolescent medicine has come into its own with the opening of the adolescent unit at Children's Hospital in Boston. Gallagher[52] believes they need a doctor of their own. "We're concerned with what all fields of medicine can do for this age group." He disclaims any intention to create another specialty in medicine.

Children comprise only 10% of all diabetics, but 40% of coma admissions to the George Baker Clinic in Boston are juveniles. While children are more susceptible to coma, the same criteria apply in prevention of it, that is, avoidance of infections, severe trauma or sunburn, and emotional upheavals. Strict adherence to insulin and a well balanced, nutritious diet are of utmost importance.

Significant atherosclerotic changes appear in diabetic children much sooner than in a non-diabetic child. Most juveniles show some changes in the retinae or kidney vessels after 10 years of the disease. Arterial degeneration has been found to be more common in the children of diabetic mothers than in a control group without diabetic parents.

The pathology of the diabetic age group we are discussing is believed to be extra-pancreatic in type.[53] All of our juvenile patients are being currently studied for glandular imbalance. We do not have the problem of obesity here, but vascular change has been seen in the conjunctiva in children of diabetic mothers.[54] Glucose tolerance tests, abnormal growth and development, and elevated 17-ketosteroid excretion were definitely correlated by these authors with the conjunctival findings. However, they admit that their series is from too small a number of patients to be finally conclusive.[54]

Although we think of juvenile diabetes as extra-pancreatic, there has been a statement made recently that growth hormone may stimulate glucagon (HGF).[55] An excess of the latter is thought to be present in juvenile diabetes. It is produced in the islet alpha cells and its chief function is to release glucose from glycogen. Gerber[56] says that growth hormone stimulates the pancreatic islet cells, and may be responsible for some cases of diabetes mellitus. He thinks that this is especially so in the "teen-age" group with its explosive onset and unstable course.

SUMMARY

1. Another case of identical twins with diabetes mellitus is reported.
2. The variance in the course of disease in identical twins is well known. This is one of the few differences in identical twins. The diabetes developed in the same season of the year, probably at the same time.
3. The twins were treated by the compatible hyperglycemia method of control established by Sindoni.[57] Postprandial blood sugars were used as a guide in control of the disease.
4. The method of diagnosing similarity in twins was discussed. Newman states that the similar appearance and finger prints are the most reliable of ten rules he requires to identify identical twins. In the finger print patterns the main lines of finger and palm prints must be essentially the same. Our twins met these qualifications.
5. The influence of heredity on the development of diabetes mellitus and its modification by environment is discussed in some detail.
6. Means of improving the life expectancy of juvenile diabetics by prevention of non-diabetic and diabetic causes of death are discussed.

CONCLUSIONS

1. Diabetes mellitus occurs in identical twins. While it often occurs simultaneously, it does not have to, because environmental factors and cytoplasmic asymmetry[58] upset the law of heredity. Sometimes only one identical twin develops the disease.
2. The effect of environmental factors and cytoplasmic asymmetry on the hereditary nature of diabetes mellitus in twins is such that the disease, if developed in both twins, may not run the same course. In this case, one 15 year old twin is on insulin and diet; the other on diet alone for 18 months, is now on insulin.
3. The major environmental influence on the hereditary tendency in adult diabetes is obesity. Since 9 out of 10 diabetics over 21 are obese[53] at the onset of the disease, this influence can largely be eliminated by advising the relatives of diabetics to lose weight immediately.
4. Since diabetes tends to breed out of generations, being a recessive gene, this procedure of reducing the obese relative if followed in medical practice, could greatly reduce the incidence of the disease.
5. Many other diseases have concordantly occurred in identical twins. This gives the medical and allied sciences an exceptional opportunity to study the factors which alter the hereditary tendency. Traits determined by heredity and modified by environmental influences are not passed on to succeeding generations.
6. Removal of the environmental factor of obesity in newly discovered diabetics may result in apparent cure[30] (at least in so far as the hyperglycemia is concerned).
7. Considering the recent studies on the prevalence of abnormal glucose tolerance tests in relatives of diabetics and the findings of blood vessel disease in the conjunctiva of children of diabetic parents, it would seem to be advisable to do post-prandial (2 hour) blood sugars on all relatives of diagnosed diabetics.
8. The use of the compatible hyperglycemia[57] method of control of diabetes will avoid insulin shock, inspire cooperation of the patient, and allow full development of juvenile nutritional needs. If it is used in conjunction with the avoidance of diabetic coma and other diabetic associated conditions, plus prevention of non-diabetic causes of death, e.g., accidents, the life expectancy of juvenile diabetics can be greatly prolonged.

Acknowledgments: To T. V. Hynes, M.D. and H. A. Tarrant, M.D. of the Department of Metabolism Staff, to the Diabetic Clinic Nursing Staff and to the Laboratory of the hospital for the special care and studies needed on the twins; also to Mr. Charles Schwarz and Sister Mary Euphrasia, O.S.F., R.N., Superintendent of St. Francis Hospital, for the photography, and to Miss Ann Moran, Record Librarian, for assistance in preparation of the scientific material of this paper. We are also greatly obliged to Captain Charles E. Bryan, Jr., Chief of Identification, Detective Division, Wilmington Police Department, for his kindness and cooperation in the taking and reading of the fingerprints.

Dr. James W. Butler, the twins' family physician and Dr. Italo Charamella were also very helpful with their advice and constructive suggestions.

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THE COLLAGEN DISEASES

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Among the disorders of the locomotor systems the rheumatic diseases are the most frequent. Under this general classification are included the disturbances that produce stiffness, soreness, and pain in some part of the musculoskeletal system. In addition to the conditions discussed below, rheumatic fever and the rare disorders, lupus erythematosis, periarteritis nodosa, dermatomyositis, and scleroderma may properly be included among the rheumatic disorders because they are all characterized pathologically by a type of fibrinoid degeneration of collagen which is similar to that seen in rheumatoid arthritis.[1]

The collagen diseases are characterized by abnormalities of the connective tissue of the body. Perhaps it would be better to call these diseases "the sterile inflammations," since they have both sterility and inflammation in common. On the other hand, these diseases may involve tissues not of mesenchymal origin, and collagen is by no means the only element of connective tissue they affect.[2]

NORMAL AND ABNORMAL CHEMO-PHYSIOLOGY

A review of the normal proliferation of the fibroblasts of clean incised wound healing gives some hint as to the cause of the fibrinoid degeneration of collagen.

The edges of the wound very soon show that they are under the influence of a stimulant. Two types of cells divide actively, the connective tissue cell and the vascular endothial cell. In both mitotic figures may be seen, particularly in the former. The connective tissue cell or fibrocyte of adult fibrous tissue is little more than a narrow nucleus surrounded by a thin layer of cystoplasm and wedged between dense bundles of collagen figers, but it rapidly changes into a plump fusiform cell with a large nucleus and well-developed cytoplasm, which may end in branching processes. The sudden change from complete quiescence to extreme activity denotes the action of a powerful stimulant.[3]

From the work of Dr. Hans Selye and his team of biologists, at the Institute of Experimental Medicine and Surgery, came the discovery that the animal organism possesses a general defense mechanism which it mobilizes against any damage,

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whatever the cause. The principal agent of the mechanism is the endocrine system. The pituitary and adrenal glands, being the most important, send their hormones into the general circulation to stimulate the delicate enzyme and coenzyme system to activate the proliferation of fibroblasts (alarm reaction).

A study of the chemistry of the blood of patients suffering with rheumatoid arthritis and rheumatic fever, the two chief collagen diseases, reveals that there is a systematic response to a stimulus whether bacterial, foreign protein, or stressor condition.

Russel Cecil, in his Text Book of Medicine gives the following abnormal findings in the blood of these patients. They have moderate leukocytosis. The Schilling hemogram frequently shows increase of immature cells; the sedimentation rate is increased, and also the albumin-globulin ratio is altered, with relative increase of globulin.[4]

M. Bodansky[5] has shown an increase of hyaluronic acid in blood of patients with acute and active rheumatic fever and rheumatoid arthritis. Kelly, Good and McQuarrie[6] observed that the serum of children with rheumatic fever contained increased concentrations of mucoprotein, a compound of protein and polymerized hyaluronic acid. This increased hyaluronic acid is not specific for rheumatic infections but is also found in lipoid nephrosis, acute poliomyelitis, non-bacterial pneumonia.

In the main two pathological processes can appear in a joint: one is inflammation, the other is degeneration. The prototype of the first is the pyogenic joint, or inflammatory joint due to unknown cause, such as in rheumatoid arthritis. The prototype of the second is seen in degenerative joint disease associated with wear and tear.

When inflammation is present the protein content of the fluid is increased. There is an increased connective tissue growth with the formation of scar tissue. In the joint the scar tissue is called pannus and may suffocate the cartilage by interfering with its nutrition from above and from below. The scarring may lead to fibrous ankylosis, and, if cartilage is completely destroyed, to bony ankylosis as well.[7]

In the rheumatoid arthritic patient the synovial fluid is increased as well as the hyaluronic acid content. The studies of Meyer[8] and his co-workers have shown that mycin is a hyaluronic acid and is largely responsible for the high viscosity of the synovial fluid.

Ragan[9] and his associates have shown that the ratio of the logarithm of the relative viscosity to the concentration of hyaluronic acid in the joint fluid ranged between 10.4 and 20.9 in 13 normal fluids. In the fluids from patients with rheumatoid arthritis the ratio ranged from 4.2 to 13.8, with most values below 8.1. There is a correlation between the value of the ratio and the severity of the arthritis. Patients with ratios below 8.1 had some evidence of acute illness.

The amount of fluid in the knee joint of patients with active disease was usually about 50-70 cc., as contrasted with 2-5 cc. in a normal knee joint. It would, therefore, appear that in rheumatoid arthritis there is an increased production of hyaluronic acid, but such hyaluronic acid is less polymerized than that from the synovial fluid of normal individuals.[10]

The elevated hyaluronic acid in the joints of patients suffering with rheumatoid arthritis is of great significance. The fact that much of the elevated hyaluronic acid is polymerized or denatured is evidence of an active response of the body to overcome the harmful effect of hyaluronidase. The elevated hyaluronidase of inflamed rheumatic tissue is an enzyme that weakens or dissolves intercellular cement to permit swelling, edema and reduced circulation by dispersing or disaggregating hyaluronic acid.[11] Since working along chemical lines, Meyer[12] and his associates showed hyaluronidase is hydrolyzed hyaluronic acid.

There has long been a search for a natural-occurring antagonist of hyaluronidase. Hartmann[13] and his associates showed that glucuronic acid, which has been found to be deficient in rheumatic

disorders, inhibits hyaluronidase; a connective tissue deteriorating enzyme showing increased activity in the serum of rheumatic patients.[14] This little known glucuronic acid is one of the intermediate products of sugar metabolism. It has definite detoxicating powers and has shown promise in arresting arthritic changes.[15]

To go a step further into the abnormal chemophysiology of rheumatoid arthritis we must, in all honesty, mention the relation between hyaluronic acid and the collagen fibrils. From all available sources, apparently the fibrils and hyaluronic acid work in close association to form the interstitial matrix or cement material which holds the extra-cellular fluids in a delicate balance to prevent edema formation. The electronic microscope has opened an entirely new world of the internal structure of the collagen fiber; by the use of this instrument and proper technique and staining methods the propagation and synthesis of the fibril has been studied.[16]

The current theory as to the formation of these mysterious fibers is summarized as follows: the fibroblasts elaborate certain proteins or enzymes necessary for collagen formation. While collagen fibrils may form within the body of the fibroblasts, they can probably also form outside of it. As the collagen is elaborated from precursors fine filaments are formed which unite longitudinally, and laterally, to produce the fibrils somewhat after the manner of crystal formation. The component filaments of the fibril appear to line themselves up in register so that the cross bands extend the full width of the fibril. This phenomenon also occurs when fibrils unite to form a fiber.

SUMMARY

The collagen disorders are of a systemic nature, and do not involve just one particular organ system. The chemical study of the blood serum of patients suffering from these diseases would logically lead one to believe that the liver, through its altered metabolism, directly contributes to the production of pathological manifestations of these disorders. To review the material presented: there is usually an elevated sedimentation rate, altered albumin-globulin ratio, and an increase of hyaluronic acid — all evidence of a hyperfunction of the liver's protein metabolism.

During severe shock many of the hepatic enzymes are inactivated and this may contribute to the general systematic damage.[17] In the conversion of glucose to glycogen there must be produced glucoronic acid, to conserve energy which would otherwise be lost, but with inactivation of the general hepatic enzyme system this cannot take place, hence there is a depletion of the body's available glucoronic acid. Also the glucoronic acid that is produced is partially inactivated by B-glucoronidase, which is increased in a stressor state. Various toxic substances increase B-glucoronidase activity in the liver and other organs. Since this is true even after treatment with substances unlikely to form glucoronides, the response has been considered to be related with non-specific tissue injury or repair.[18]

CONCLUSION

In conclusion, it may be stated that the collagen diseases are systematic in nature; that the liver through its altered protein metabolism influences the production of protein substances which give rise to the characteristic pathologic processes of collagen disorders; and that glucoronic acid, given in large enough doses intramuscularly, may possibly inhibit or reverse the harmful effect of the spreading factor hyaluronidase, hyaluronidase appearing to be the enzyme responsible for the production of the collagen changes seen in these diseases.

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CLINICAL EVALUATION OF APPETITE DEPRESSANTS

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Obesity and its complications are recognized as important problems affecting the health of a large segment of our population.

Among insured persons, Dublin and Marks[1] found a marked increase in mortality in those who were overweight. While it is true that a large number of the obese are attempting some dietary restriction, either for medical or esthetic reasons, only a small number will lower their weight to near the normal range.

Emotional or metabolic factors[2] undoubtedly play a role in many cases, but it is generally agreed that the average overweight person can reduce if the caloric intake is below their energy requirements. This would seem to offer a simple and ideal solution to the problem, but the numerous failures so frequently encountered point up the difficulties experienced by those who diet.

Hunger, often in proportion to previous habits of overeating, presents a major obstacle for those who desire to lose weight. For this reason, various types of appetite depressants are prescribed by the physician or purchased by the public. The present study was undertaken to determine the efficacy and safety of some of the appetite depressants currently employed as adjuncts to weight reducing diets.

Generally speaking, four types of substances are employed namely:

1. Bulk, such as methyl cellulose wafers
2. Dextro-amphetamine alone or in combination with bulk.
3. Lozenges containing vitamins and minerals.
4. Low calorie candy containing vitamins and minerals.

PROCEDURE

The present investigation included 240 overweight individuals approximately equally divided into six groups according to age, sex, activity, and degree of overweight.

Initially there were 16 more cases under study which were lost sight of during the 60 day period. Before inclusion in the study a psychological test was given to all subjects in order to exclude if possible "compulsive eaters." Also, those with organic disease and persons under 20 years of age were excluded. At the initial examination the patients' history, family traits, physical examination, B. M. R., C. B. C., and urinanalysis were completed. Each individual was re-examined at two week intervals during the test. The six groups were placed on the following regimes:

A. 1200 calorie diet and dextro-amphetamine 5 mg. tid 1/2 hr. a.c.
B. 1200 calorie diet only.
C. 1200 calorie diet and lozenges 1-2 tid 1/2 hr. a.c.
D. 1200 calorie diet and methyl cellulose wafers 1-2 tid 1/2 hr. a.c.
E. 1200 calorie diet and caramel type low calorie candy, 1-2 tid 1/2 hr. a.c. with warm water.
F. No diet, i.e., advised to generally curtail food intake, and caramel type low calorie candy 1-2 with warm water tid 1/2 hr. a.c.

In each of the above the appetite reducing aids were given according to the

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f—Brusch Medical Center, Cambridge, Massachusetts.

recommendations of the manufacturers.

The following tables give the numbers, age, and sex distribution of the six groups:

Table 1

	M	F	Total
Age under 40	16	52	68
Age over 40	34	138	172
Total	50	190	240
	M	F	Total
Less than 30% overweight	34	153	187
More than 30% overweight	16	37	53
Total	50	190	240

In the six groups the division was as follows:

Table 2

	Number	Age under 40	Age over 40	Sex M	Sex F
A.	41	11	30	8	32
B.	39	12	27	7	33
C.	40	11	29	7	33
D.	40	10	30	9	32
E.	38	13	25	9	28
F.	42	11	31	10	32
	240	68	172	50	190

At each examination the patients were questioned regarding their adherence both to the diet and to the schedule of appetite depressant.

RESULTS

There was a rather wide variation in the results observed in the various groups after 60-64 days. No correlation could be established relative to loss according to age, sex, or degree of physical activity. Within the groups wide variations also were found which, on close examination, were related to the persistence in following the prescribed regime.

The following table gives the average weight loss in each of the groups:

Table 3

A.	7.31 lbs
B.	4.90 lbs
C.	5.48 lbs
D.	6.30 lbs
E.	13.70 lbs
F.	5.92 lbs

In groups A, B, C, D, E, and F the variations in weight loss or failure to lose weight, may be attributed to four factors:

1. Unwillingness to follow the prescribed diet.
2. Insatiable appetite due to failure of the depressant to partially suppress hunger.
3. Possible intrinsic metabolic factors.
4. Emotional factors which play a large role to be calculated and reported at a later date.

Group F, on a liberal diet, lost more weight than did the 1200 calorie groups, due to many failures in these latter groups because of insatiable appetite.

In the first five groups the maximum loss by 5 persons was approximately the same, and double the average loss for the group. Some individuals actually gained weight during the test; others after a satisfactory initial loss, regained.

Among those who failed to lose weight it was found that objection by the subject to one element of the program was the controlling factor. In most instances this was related to a dislike of the depressant, either because of taste or of side effects. Acquired dislike or appearance of side effects coincided with failure to lose more weight, or with a subsequent gain.

The following table gives the number and reason for rejection of the depressant.

Table 4

Group	Discontinued	Taste	Side Effects
A.	9	0	9
C.	13	11	2
D.	8	6	2
E.	3	3	0
F.	2	2	0
Total	35	21	14

Note—No depressant was used in group B.

In group A, receiving dextro-amphetamine, nine discontinued because of nervous symptoms in the following order of frequency: nervousness, sleeplessness, and tremor.

In the remainder, taste factors were principally involved. The digestive disturbances reported were of a mild nature and possibly psychosomatic in origin. The depressant employed in groups E and F contained more calories, thereby increasing intake by 100-150 calories per day. It is possible that the sugar content of this depressant may have partially overcome the "metabolic hypoglycemia in some of these subjects".[3]

(Concluded on page 298)

Editorials

DELAWARE STATE MEDICAL JOURNAL

Owned and published by the Medical Society of Delaware, a scientific non-profit corporation. Issued the fifteenth of each month under the supervision of the Committee on Publication.

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Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, Published by the American Medical Association, Chicago.

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VOL. 26 NOVEMBER, 1954 NO. 11

THE 1954 MEETING

The 165th Annual Session of the Medical Society of Delaware was held at Dover, October 11-13, 1954, President Hewitt W. Smith, of Harrington, presiding.

A meeting of the Council was held in Wilmington on September 27th, which passed on many routine matters, thus making it possible for the meeting of the House of Delegates to proceed more quickly and more efficiently. The most important items considered had to deal with legislation and appropriations. The full transactions will be printed in the December issue of THE JOURNAL.

The scientific meetings proceeded exactly as printed in the September JOURNAL. These papers were all of a high order and were well received and adequately discussed.

The elections for the year 1955 resulted as follows:

President, Lewis B. Flinn.....Wilmington
President-elect, Glen M. Van Valkenburgh, Georgetown
Vice-President, E. Harold Mercer.....Dover
Secretary, Norman L. Cannon.....Wilmington
Treasurer, Charles Levy.....Wilmington
Rep. to D.A.M., W. Oscar LaMotte...Wilmington

The Woman's Auxiliary met at the same time under the Presidency of Mrs. Allan R. Crutchley of Middletown. The following officers for 1954-55 were elected and installed:

President, Mrs. Gerald A. Beatty....Wilmington
Pres.-Elect, Mrs. Richard W. Comegys...Clayton
Vice-Pres., Mrs. Charles M. Moyer.....Laurel
Record. Sec'y, Mrs. I. Lewis Chipman, Jr., Wilmington
Corr. Sec'y, Mrs. Stephen W. Bartoshesky, Wilmington
Treasurer, Mrs. Harold J. Laggner.....Smyrna

The social events of the Society and the Auxiliary were held according to schedule, and were enjoyed by large audiences at each. The main event was the reception and dinner on October 12th, followed by a very interesting address by U. S. Senator J. Allen Frear, Jr.

The technical exhibits were all good, and reached a new high for income at Dover. The Society is grateful to them for their financial assistance to our meeting. Ours is a small Society and an occasional comparison with a large one is illuminating. The Pennsylvania Society held their 103rd session at Harrisburg, September 21-24, 1953, with 13.9% of their membership registered. We give below the registration figures from our meeting this year:

Members	103
Guests, Visitors	38
Internes, Students	7
Exhibitors	38
Woman's Auxiliary	78
Total	264
Membership	374
% Registered	27.5

We were informed a couple of years ago that, throughout the U. S., the *average* state medical meeting showed 30-35% of their membership in attendance. We believe this figure is much too high.

So passes into history the 1954 Session. Now let us turn our faces towards Wilmington, in 1955, and make the next Session an even better one.

Clinical Evaluation

(Concluded from page 296)

In group B, receiving no depressant, it is computed that more than 1/3 of the members failed to follow the dietary restrictions imposed. Those who did remain on the diet without a dietary aid were found for the most part to be psychologically unhappy and disturbed throughout the study.

SUMMARY

The present study on 240 subjects was undertaken to assess the value of appetite depressants as an aid to a standard 1200 calorie diet. In one group — F — no diet was prescribed. The group was advised to generally curtail food intake and to use a low calorie candy type depressant.

Results indicate that:

1. Appetite depressants are of definite assistance in achieving weight loss in overweight adults.
2. Acceptability and absence of side effects of those substances are important factors in securing patient cooperation.
3. In the present study a low calorie—vitamin-mineral caramel-type candy* gave the best overall results.

*AYDS, furnished by the Campana Corporation, Batavia, Ill.

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A REQUEST

In order that the State Board of Health may act as a source of information concerning numbers of abnormal infants born in the state of Delaware, it is requested that physicians be reminded to fill in all abnormalities noted at birth in the space provided on the present birth certificate.

If physicians performing deliveries cooperate in this matter it will be a great help to the Commission for Feeble Minded.

EDWARD M. VAUGHAN, M.D.

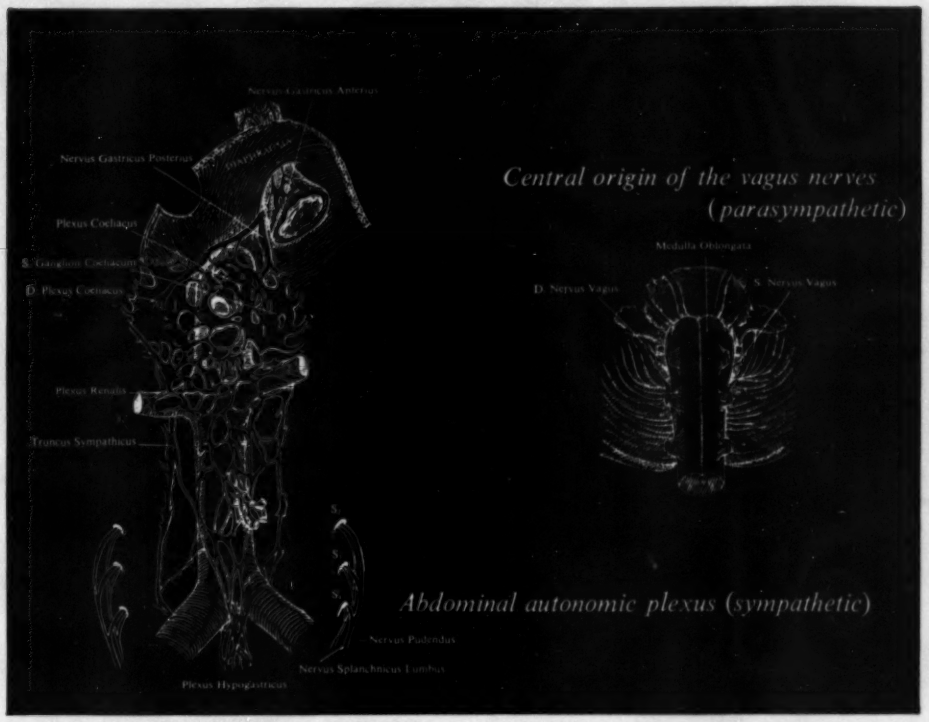
Dr. Edward M. Vaughan died at his home in Middletown on October 5, 1954, aged 81 years. The son of Edward Mitchell Vaughan and Eliza Ann Evans, he was born in Milton, April 22, 1873, and attended public schools in that community.

He was well-known as a medical man in the community, and was a leading figure in the medical selective service system of the draft during World Wars I and II. Dr. Vaughan was also a registered pharmacist and a medical doctor, having graduated from the National Institute of Pharmacy in 1900. He received his medical degree from Jefferson Medical College, Philadelphia, in 1905.

Dr. Vaughan was a vestryman and treasurer of St. Anne's Church, and a former president of Middletown Board of Health.

Survivors include his wife, Mrs. Eva C. Vaughan; a son, Henry, and several grandchildren, of Radnor, Pa.

Funeral services were held on October 7th at St. Anne's Episcopal Church, conducted by the Rev. Walden Pell II, headmaster of St. Andrew's School, and the Rev. Percy L. Donaghay, rector emeritus of the church. Internment was in St. Anne's Cemetery.



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It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association. Searle Research in the Service of Medicine.

1. Zupko, A. G.: Pharmacology and the General Practitioner, GP 7:55 (March) 1953.

2. McHardy, G. G., and Others: Clinical Evaluation of Methantheline (Banthine) Bromide in Gastroenterology, J.A.M.A. *147*:1620 (Dec. 22) 1951.

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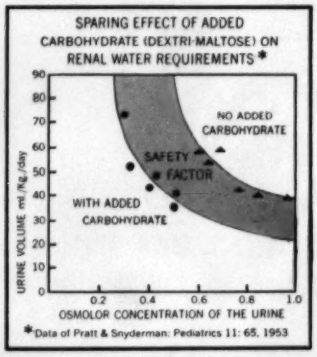

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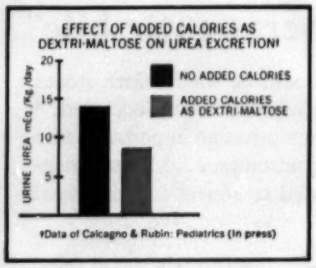
The margin of renal safety is especially important since various stresses and handicaps have been shown to influence the infant's fluid balance and renal capacity.[1,3,4,5]



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